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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/370,453	08/09/1999	DAN W. DENNEY JR.	GENITOPE-038	8128
23535	7590	08/09/2006	EXAMINER	CANELLA, KAREN A
MEDLEN & CARROLL, LLP 101 HOWARD STREET SUITE 350 SAN FRANCISCO, CA 94105			ART UNIT	PAPER NUMBER
			1643	

DATE MAILED: 08/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>
	09/370,453	DENNEY, DAN W.
	<b>Examiner</b> Karen A. Canella	<b>Art Unit</b> 1643

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on \_\_\_\_\_.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 25-29 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 25-29 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) All    b) Some \* c) None of:
    1. Certified copies of the priority documents have been received.
    2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
 Paper No(s)/Mail Date \_\_\_\_\_.
- 4) Interview Summary (PTO-413)  
 Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: \_\_\_\_\_.

### **DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 19, 2006 has been entered.

Claims 25, 28 and 29 have been amended. Claims 25-29 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-29 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims have been amended to specify a “cell expressing a multivalent composition for active idiotype immunotherapy”. Applicant argues that this limitation is supported through the specification and in particular on page 88 line 16. this has been considered but not found persuasive. When given the broadest reasonable interpretation, a “cell expressing a multivalent composition for active immunotherapy” encompasses the use of the cell itself as an immunotherapeutic, and this limitation is not described in the originally filed disclosure. Page 89, lines 14-15 state

*“methods for the production of tumor-specific Ig derived from a B cell lymphoma patient are provided”*

The specification further contemplates in lines 15-18, that the methods of the invention can be modified for the production of soluble TCR for treatment of T cell tumors, or the production of Ig for the treatment of B cell leukemias. Thus there is no support in the specification as filed for the administration of the entire recombinant cell for active idiotype immunity. One of skill in the art would reasonable conclude that applicant was not in possession of the broadly claimed cell, wherein the cell itself was to be used in immunotherapy.

The rejection of claims 25-29 under 35 U.S.C. 103(a) as being unpatentable over Cleary et al (Cell, 1986, Vol. 44, pp. 97-106) in view of Levy et al (Journal of Experimental Medicine, 1988, Vol. 168, pp. 475-489) and Embleton et al (Nucleic Acids Research, 1992, Vol. 20, pp. 3831-3837) is maintained for reasons of record..

Claims 25, 28 and 29 are drawn to a cell expressing a multivalent composition for active idiotype immunotherapy produced by insertion of isolated nucleic acids from malignant B-cell lymphoma into an expression vector, wherein said isolated nucleic acids comprise nucleotide sequences encoding at least one V<sub>h</sub> region and at least two V<sub>h</sub> regions, nucleotide sequence encoding at least two V<sub>h</sub> regions and at least one V<sub>l</sub> region or nucleotide sequence encoding at least two V<sub>h</sub> regions and at least two V<sub>l</sub> regions, wherein said at least two V<sub>h</sub> regions and said at least two V<sub>l</sub> regions differ by at least one idiotope. Claims 26 and 27 embody the composition of claim 25 wherein the nucleotide sequence encoding said V<sub>h</sub> and V<sub>l</sub> regions comprise at least two V<sub>h</sub> and one V<sub>l</sub> region, and at least two V<sub>l</sub> and one V<sub>h</sub> region, respectively.

Section 2113 of the M.P.E.P. states:

PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS  
"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

When given the broadest reasonable interpretation, a cell expressing a multivalent composition for active immunotherapy encompasses both the direct use of the cell in immunotherapy as well as using the cell to produce a soluble multivalent composition. The following rejection applies to using the recombinant cells to secrete the soluble multivalent composition.

Cleary et al teach instance of patients whose B cell tumors escaped the therapeutic effects of a monoclonal anti-idiotype antibody because of the emergence of subclones that showed changes in their Ig idiotypes (page 97, second column, lines 36-39). Cleary et al suggest that the idiotype heterogeneity unmasked by the anti-idiotype therapy resulted from somatic mutations within the variable region because the variant subclones were derived from the same original clone of neoplastic B-cells, and the same patterns of bands for rearranged Ig genes were detected (page 97, second column, lines 40-47). To confirm this hypothesis, Cleary et al cloned and sequences the functional heavy chain Ig genes from multiple independent isolates of a patients tumor cell population to conclude that point mutations in the variable regions accounted for the loss of idiotype following antibody therapy (page 97, second column, lines 48-54 and page 103, first column, lines 1-6 under the heading "Discussion"). Cleary et al also teach a marked heterogeneity in the variable region sequences of the tumor cell population prior to anti-idiotype therapy, having significant clustering of amino acid substitutions in CDR2 (page 97, second column, line 54 to page 98, first column, line 3 and page 103, second column, lines 26-28). Cleary et al teach that the clustering of mutation in the CDR2 after anti-idiotype therapy can be attributed in part to the strong negative selection exerted by the 7D11 antibody (page 104, first column, first paragraph). Cleary et al do not teach a multivalent idotypic vaccine which would comprise the variant V<sub>H</sub> sequences which would comprise more than one idiotype and variant V<sub>L</sub> sequence which would comprise more than one idiotype.

Levy et al corroborates the teaching of Cleary et al regarding the V<sub>H</sub> sequences from multiple isolated of human B cell lymphoma (page 475, lines 19-23) and further teach that the light chain genes of human lymphoma cells mutate independently from heavy chain genes (page 476, lines 7-13).

Embleton et al teach in-cell PCR allowing for the linking and amplification of the expressed Vh and Vl within a single B-lymphocyte in order to preserve the particular combination of Vh and Vl within a lymphocyte (page 3831, second column, lines 17-18). Embleton et al teach that this method is superior to the prior art methods of PCR cloning of Ig regions which lost the natural combination of the heavy and light chains and required artificial recombination which had the potential to be dominated by promiscuous chains leading to different affinities and specificities (page 3831, second column, lines 8-16).

It would have been *prima facie* obvious to one of skill in the art at the time the invention was made to make a multivalent composition for idiotypic vaccination of a patient having a B-cell lymphoma by amplifying and linking the Vh and Vl chains of a multitude of B-lymphoma cells and recombinantly expressing the recombinant variable chains while retaining the original combinations of heavy and light chains in host cells. One of skill in the art would have been motivated to do so by the teachings of Cleary et al on the emergence of malignant B-cells which escaped anti-idiotype therapy due to somatic mutations with the variable regions and the evidence presented by Cleary regarding the existence of heavy chain heterogeneity before the anti-idiotype therapy; the teachings of Levy et al on the presence of heterogeneity in the light chain of human B-cell lymphomas, and the teachings of Embleton regarding improvements in the PCR cloning of immunoglobulin genes from B-lymphocytes which preserves the natural paring of heavy chain and light chain and avoids the problems associated with the screening of artificial combinations. One of skill in the art would have been motivated to include a multitude of natural combinations of Vh and Vl sequences from the patients B-cell lymphomas in order to insure that an immune response could be raised to more than just one population of B-cells having a specific combination of Vh and Vl sequences because although it is evidence that a single clonal event precipitated the B-cell lymphoma, somatic mutations accumulate within both the heavy and light chains of the lymphoma

Applicant argues that none of the references teach or suggest individual transformed cells or clones which express combinations of variant Vh or Vl sequences as recited by the present claims. This has been considered but not found persuasive. The instant claims require the isolation of a transformed cell comprising

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at least one Vh region and at least two Vl regions;  
at least two Vh regions and at least one Vl region;  
at least two Vh regions and at least two Vl regions;  
wherein said at least two Vh regions and at least two Vl regions differ by at least one idiotope.

The claim does not require the scrambling of Vh regions and Vl regions, so as to produce Vh regions and Vl regions that do not associate in the same manner as that originally found in the patient. The claim only requires that the multivalent composition of expressed Vh and Vl represent at least one different idiotope. Applicant is reminded that the examiner is interpreting the claims as product by process claims. A multivalent composition comprising secreted Ig reflecting the idiotypic variation found in the patient would be the same as that claimed regardless of whether or not it came from a single clone expressing the alternate idiotope or a multitude of different clones encompassing the alternate idiotope. Thus, it is concluded that Embleton et al does not teach against the instant claims as there is ample motivation to include a multitude of different clones processed by the method of embleton in order to provide a spectrum of clones reflecting the diversity of the Ig found in the patient having quasi-clonal B cell lymphoma.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.  
8/6/2006



KAREN A. CANELLA PH.D  
PRIMARY EXAMINER